

## General

### Guideline Title

Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report.

### Bibliographic Source(s)

Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, Palevsky HI, Rich S, Sood N, Rosenzweig EB, Trow TK, Yung R, Elliott CG, Badesch DB. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest. 2014 Aug;146(2):449-75. [90 references] [PubMed](#)

### Guideline Status

This is the current release on the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

The grades of recommendation (1A–2C, CB) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

#### Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults

1. The panel suggests that the severity of a pulmonary arterial hypertension (PAH) patient's disease be evaluated in a systematic and consistent manner, using a combination of World Health Organization (WHO) functional class (FC), exercise capacity, echocardiographic, laboratory and hemodynamic variables in order to inform therapeutic decisions (Grade CB).
2. The panel suggests that, whenever possible, all PAH patients be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy (Grade CB).
3. The panel suggests collaborative and closely coordinated care of PAH patients involving the expertise of both local physicians and those with expertise in PAH care (Grade CB).

*Remark:* Appropriate care may require the coordinated efforts of cardiologists, pulmonologists, rheumatologists, primary care, or other specialties.

#### Treatment Naive PAH Patients without Symptoms (WHO FC I) and Patients at Increased Risk for the Development of PAH

4. For treatment naive PAH patients with WHO FC I symptoms, the panel suggests continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy (Grade CB).

5. The panel suggests that patients at risk for the development of PAH (e.g., patients with systemic sclerosis or the presence of a known mutation placing the patient at risk for PAH) be monitored for the development of symptoms of PAH (Grade CB).

6. The panel suggests also that contributing causes of PH (e.g., sleep apnea and systemic hypertension) in patients with PAH be treated aggressively (Grade CB).

### Symptomatic Patients with PAH

#### Vasoreactivity Testing and Use of Calcium Channel Blockers

7. The panel suggests that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing (Grade CB).

*Remark:* Contraindications to acute vasoreactivity testing include a low systemic blood pressure, low cardiac output or the presence of FC IV symptoms. Acute vasoreactivity testing may be complicated by hypotension, and the misinterpretation of results may result in the inappropriate exposure of patients to the risks of a treatment trial with calcium channel blockers (CCBs) without the possibility of clinical benefit. Vasoreactivity testing should be performed by individuals with appropriate training in test performance and interpretation.

8. The panel suggests that patients with PAH who, in the absence of right-heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB blocker (Grade CB).

9. The panel suggests that CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity (Grade CB).

### PAH-Specific Pharmacotherapies

#### Patients with WHO FC II Symptoms

For treatment naive PAH patients with WHO FC II symptoms who are not candidates for, or who have failed CCB therapy, the panel advises monotherapy be initiated with a currently approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:

10. The panel recommends ambrisentan to improve 6-min walk distance (6MWD) (Grade 1C).

11-12. The panel suggests bosentan to delay time to clinical worsening (Grade CB) and improve cardiopulmonary hemodynamics.

13. The panel suggests macitentan to delay the time to clinical worsening (Grade CB).

14. The panel recommends sildenafil to improve 6MWD (Grade 1C).

15. The panel suggests tadalafil to improve 6MWD (Grade CB).

16-19. The panel suggests riociguat to improve 6MWD (Grade CB), improve WHO FC (Grade CB), delay the time to clinical worsening (Grade CB) and improve cardiopulmonary hemodynamics.

20. The panel suggests also that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naive PAH patients with WHO FC II symptoms or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals (Grade CB).

#### Patients with WHO FC III Symptoms

For treatment-naive PAH patients with WHO FC III symptoms who are not candidates for, or who have failed CCB therapy, the panel advises monotherapy be initiated with a currently approved ETAR, a PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:

21. The panel recommends the use of bosentan to improve 6MWD (Grade 1B).

22-23. The panel suggests the use of bosentan to decrease hospitalizations related to PAH in the short-term (Grade 2C), and to improve cardiopulmonary hemodynamics.

24. The panel recommends the use of ambrisentan to improve 6MWD (Grade 1C).

25-26. The panel suggests macitentan to improve WHO FC (Grade CB) and delay the time to clinical worsening (Grade CB).

27-29. The panel recommends the use of sildenafil to improve 6MWD (Grade 1C) and to improve WHO FC (Grade CB). The panel suggests the

use of sildenafil to improve cardiopulmonary hemodynamics.

30-33. The panel suggests the use of tadalafil to improve 6MWD (Grade CB), to improve WHO FC (Grade CB), to delay time to clinical worsening (Grade CB) and to improve cardiopulmonary hemodynamics.

34-37. The panel suggests riociguat to improve 6MWD (Grade CB), improve WHO FC (Grade CB), delay the time to clinical worsening (Grade CB) and improve cardiopulmonary hemodynamics.

For treatment naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, the panel advises consideration of initial treatment with a parenteral prostanoid. More specifically in these patients:

38-40. The panel suggests continuous intravenous (IV) epoprostenol to improve FC (Grade CB), improve 6MWD (Grade CB), and improve cardiopulmonary hemodynamics.

41. The panel suggests continuous IV treprostinil to improve 6MWD (Grade CB).

42-43. The panel suggests continuous subcutaneous treprostinil to improve 6MWD (Grade CB) and improve cardiopulmonary hemodynamics.

For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, the panel advises consideration of the addition of a parenteral or inhaled prostanoid. More specifically in these patients:

44-46. The panel suggests IV epoprostenol to improve WHO FC (Grade CB), improve 6MWD (Grade CB), and improve cardiopulmonary hemodynamics.

47-48. The panel suggests IV treprostinil to improve 6MWD (Grade CB) and improve cardiopulmonary hemodynamics.

49. In patients with PAH who remain symptomatic on stable and appropriate doses of an endothelin receptor antagonist (ETRA) or a PDE5 inhibitor, the panel suggests the addition of inhaled treprostinil to improve 6MWD (Grade 2C).

*Remark:* The usual initial dose of inhaled treprostinil is 3 inhalations (18 µg) every 6 h. However, optimal effect of inhaled treprostinil may require titrating treprostinil doses up to 9 inhalations (54 µg) every 6 hours.

50-51. In patients with PAH who remain symptomatic on stable and appropriate doses of an ETRA or a PDE5 inhibitor, the panel suggests the addition of inhaled iloprost to improve WHO FC (Grade CB) and delay the time to clinical worsening (Grade CB).

#### Patients with WHO FC IV Symptoms

For treatment naive PAH patients in WHO FC IV, the panel advises initiation of monotherapy with a parenteral prostanoid agent. More specifically in these patients:

52-54. The panel suggests continuous IV epoprostenol to improve WHO FC (Grade CB), improve 6MWD (Grade CB), and improve cardiopulmonary hemodynamics.

55. The panel suggests continuous IV treprostinil to improve 6MWD (Grade CB).

56-57. The panel suggests continuous subcutaneous treprostinil to improve 6MWD (Grade CB) and improve cardiopulmonary hemodynamics.

For treatment naive PAH patients in WHO FC IV who are unable or do not desire to manage parenteral prostanoid therapy, the panel advises treatment with an inhaled prostanoid in combination with an ETRA. More specifically in these patients:

58-59. The panel suggests bosentan to improve 6MWD (Grade 2B) and cardiopulmonary hemodynamics.

60-61. The panel suggests inhaled iloprost to improve 6MWD (Grade CB), and improve WHO FC (Grade CB).

62. The panel suggests inhaled treprostinil (in combination only) to improve 6MWD (Grade CB).

#### PAH Patients on Established PAH-Specific Therapy

63. In PAH patients initiating therapy with IV epoprostenol, the panel suggests against the routine simultaneous initiation of bosentan (Grade CB).

For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, the panel advises addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the evaluation and

treatment of complex patients with PAH. More specifically:

64. In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, the panel suggests the addition of inhaled iloprost to improve 6MWD (Grade CB).

65. In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, the panel recommends the addition of inhaled treprostinil to improve 6MWD (Grade 1C).

*Remark:* The usual initial dose of inhaled treprostinil is 3 inhalations (18 µg) every 6 h. However, optimal effect of inhaled treprostinil may require titrating treprostinil doses up to 9 inhalations (54 µg) every 6 hour.

66. In PAH patients who remain symptomatic on stable doses of established IV epoprostenol, the panel suggests the addition of sildenafil or up titration of epoprostenol to improve 6MWD (Grade CB).

67-70. In patients with PAH who remain symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, the panel suggests the addition of the soluble guanylate cyclase stimulator riociguat to improve 6MWD (Grade CB), WHO FC (Grade CB) and cardiopulmonary hemodynamics and to delay the time to clinical worsening (Grade CB).

71-73. In patients with PAH who remain symptomatic on stable doses of a PDE5 inhibitor or an inhaled prostanoid, the panel suggests macitentan to improve 6MWD (Grade CB), WHO FC (Grade CB) and to delay the time to clinical worsening (Grade CB).

74. For WHO FC III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy, the panel suggests addition of a third class of PAH therapy (Grade CB).

*Remark:* Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH.

#### Specific Patient Situations

##### Pregnancy

75. In patients with PAH, the panel suggests that pregnancy be avoided (Grade CB).

*Remark:* Estrogen-containing contraceptives may increase the risk of venous thromboembolism (VTE) and are not recommended for women with childbearing potential who have PAH. Additionally, the ETRA bosentan may decrease the efficacy of hormonal contraception. Bosentan, ambrisentan, macitentan and riociguat are contraindicated in pregnancy (category X; evidence of serious fetal abnormalities) and dual mechanical barrier contraceptive techniques are recommended in female patients of childbearing age taking these medications.

76. When pregnancy does occur, the panel suggests care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension, the high-risk obstetrical and cardiovascular anesthesiology services (Grade CB).

##### Altitude and Air Travel

77. In patients with PAH, the panel suggests that exposure to high altitude be avoided, and that supplemental oxygen be used as needed during altitude exposure or air travel to maintain oxygen saturations greater than 91% (Grade CB).

*Remark:* Patients with borderline oxygen saturations at sea level may require 3-4 L per minute of supplemental oxygen under these conditions, and those already using supplemental oxygen at sea level should increase their oxygen flow rate on commercial aircraft.

##### Vaccinations

78. In patients with PAH, the panel suggests maintaining current immunization against influenza and pneumococcal pneumonia (Grade CB).

##### Surgery

79. In patients with PAH, the panel suggests avoiding nonessential surgery, and when surgery is necessary the panel suggests care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension team, the surgical service, and cardiovascular anesthesiology with careful monitoring and management of clinical status, oxygenation and hemodynamics postoperatively (Grade CB).

#### Definitions:

##### Strength of the Recommendations Grading System

Grade of Recommendation	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence, Grade 1C	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient's or societal values. Further research is very unlikely to change confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient's or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Weak recommendation, low- or very-low-quality evidence, Grade 2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate
Consensus-based, Grade CB	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate

## Clinical Algorithm(s)

None provided

## Scope

## Disease/Condition(s)

Pulmonary arterial hypertension (PAH)

## Guideline Category

Management

Treatment

# Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Pharmacology

Pulmonary Medicine

Rheumatology

## Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

To provide clinicians advice regarding pharmacologic therapy for adult patients with pulmonary arterial hypertension (PAH) as informed by available evidence

## Target Population

Adult patients with pulmonary arterial hypertension (PAH)

## Interventions and Practices Considered

1. Evaluation of pulmonary arterial hypertension (PAH) severity (combination of World Health Organization [WHO] functional class [FC], exercise capacity, echocardiographic, laboratory and hemodynamic variables)
2. Treatment at a pulmonary hypertension center using a multidisciplinary approach
3. Monitoring of symptoms
  - Treatment naïve patients without symptoms (WHO FC I)
  - Patients at increased risk for development of PAH
4. Vasoreactivity testing using a short-acting agent
5. Trial of calcium channel blocker (CCB) therapy (in acute vasoreactivity)
6. PAH-specific pharmacotherapies
  - Endothelin receptor antagonists (ETRA) (bosentan, ambrisentan, macitentan)
  - Phosphodiesterase-5 (PDE5) inhibitors (sildenafil, tadalafil)
  - Soluble guanylate cyclase stimulator (riociguat)
  - Prostanoids (epoprostenol, treprostinil, iloprost)
7. Consideration of specific patient situations
  - Avoidance of pregnancy and estrogen-containing contraceptives
  - Avoidance of high altitudes and use of supplemental oxygen during air travel
  - Maintenance of influenza and pneumococcal pneumonia vaccinations
  - Avoidance of nonessential surgery

## Major Outcomes Considered

- Effectiveness of pharmacotherapies
- Intermediate-term outcomes, such as hemodynamic parameters, dyspnea, and 6-min walk distance (6MWD)
- Long-term outcomes, such as functional class, quality of life, right-sided heart failure or right ventricular dysfunction, and mortality
- Adverse effects of pharmacotherapies

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### Identifying and Reviewing the Evidence

##### Key Questions and Systematic Search

The guideline expert panel used the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Report titled "Pulmonary Arterial Hypertension: Screening, Management, and Treatment" (see the "Availability of Companion Documents" field) and chose to focus the development of a guideline document exclusively on one of the three key questions (key question 3) in the report: "For patients with pulmonary arterial hypertension (PAH), what are the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium channel blockers, prostanoids, endothelin antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?" As standard practice for the AHRQ, this key question was posted for public comment for 30 days, and later the draft report also was open for public remarks.

For key question 3, the systematic review of the literature was performed by the Duke University Evidence-Based Practice Center (EPC) for AHRQ. Search strategies were developed by the EPC using the National Library of Medicine's medical subject headings keyword nomenclature developed for MEDLINE and adapted for other databases. The EPC searched MEDLINE via PubMed, EMBASE, and the Cochrane Library from 1990 to April 2013, and limited to English language papers and randomized controlled trials (RCTs). Manual searches also supplemented the electronic searches. Refer to Appendix A of the AHRQ Comparative Effectiveness Report for the exact search strategies used.

Following completion of the EPC-conducted literature review, the endothelin receptor antagonist (ETRA) macitentan and the soluble guanylate cyclase stimulator riociguat were approved by the U.S. Food and Drug Administration (FDA) for the treatment of PAH, and so the panel completed literature searches to identify randomized controlled trials (RCTs) of their use. A key question was formulated in a similar format: "For patients with PAH, what are the comparative effectiveness and safety for PAH using macitentan or riociguat on intermediate-term and long-term patient outcomes?" Search strategies also included medical subject headings keyword nomenclature to search MEDLINE via PubMed and the Cochrane library from 2003 to October 2013, and limited to English language papers and RCTs. Manual searches also supplemented the electronic searches. All gathered references were imported into an electronic database (EndNote <sup>®</sup> 6; Thomson Reuters) in an electronic folder specific to pharmacotherapy type.

##### Study Selection

PICOTS (Population, Intervention, Comparator, Outcome, Timing, and Setting) criteria (see Table 1 in the original guideline document) were used by the EPC to select articles for inclusion at both the title and abstract and full-text screening stages. Titles and abstracts were examined independently by two reviewers from the EPC for potential relevance. Articles included by the reviewers underwent full-text screening, in which paired researchers from the EPC independently reviewed articles and indicated which ones to include for data extraction. Any disagreements were reconciled through a third party arbitrator at the EPC. All screening decisions were made and tracked in the DistillerSR database (Evidence Partners).

In the literature search performed by the EPC, there were 8,256 citations gathered (3,919 MEDLINE, 36 Cochrane, 4,301 EMBASE). After 1,626 duplicate articles were removed and 46 articles were added manually, a total of 6,676 citations were identified. The screening of abstracts excluded 5,352 articles, and the inclusion criteria excluded 1,127 additional articles. The remaining 197 articles representing 186 unique studies passed full-text screening. Of these, 46 articles (37 studies) were relating to monotherapy or combination therapy for PAH using prostanoids, endothelin antagonists, or phosphodiesterase inhibitors. The search for RCTs of the use of calcium channel blockers (CCBs) for the therapy for PAH found no studies. Because CCBs continue to be used and play an important role in the therapy for a small subset of patients with PAH, the guideline panel chose to develop consensus statements on the basis of available nonrandomized studies in this one class of drugs to provide clinically helpful advice for their use.

For the review performed for macitentan and riociguat, there were four citations gathered for macitentan and four citations gathered for riociguat. After the same PICOTS criteria was used by the panel to select articles for inclusion at both the title and abstract and full-text screening stages, one study remained for macitentan and one study remained for riociguat.

## Number of Source Documents

46 articles (37 studies) were found relating to monotherapy or combination therapy for pulmonary arterial hypertension (PAH) using prostanoids, endothelin antagonists, or phosphodiesterase inhibitors. For the review performed for macitentan and riociguat, one study remained for macitentan and one study remained for riociguat.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used for summarizing and grading the pooled evidence. See the "Rating Scheme for the Strength of the Recommendations" field.

## Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Data Extraction and Quality Assessment

Based on the included studies, the panel constructed data tables that summarized key data elements of each included article. Data elements in the tables included sample size and description, setting description, intervention name and dose, outcome name and values, and associated significance levels.

The critical appraisal quality score of each individual study was determined from the Evidence-Based Practice Center (EPC) based on the Cochrane Risk of Bias tool. Two raters from the EPC independently evaluated each study, and differences were resolved by consensus. Summary ratings of good, fair, or poor were assigned to each individual study by the EPC based on the tool (see the "Rating Scheme for the Strength of the Evidence" field). For the two articles included from the panel review of macitentan and riociguat, the panel used the same Cochrane Risk of Bias tool to assess study quality. The panel placed the quality scores for each included article as another data element in the constructed data tables.

Meta-analyses and Pooling of Outcomes

The data extracted by the panel in the evidence tables from the included studies were pooled according to comparable interventions and outcomes. The panel included only those studies that addressed the use of therapies currently approved by the U.S. Food and Drug Administration (FDA).



A meta-analysis using random effects was performed by the panel methodologist to quantitatively synthesize available outcome data by intervention. The relative effects for pooled studies were estimated using an odds ratio (OR) for discrete outcomes and mean difference for continuous outcomes. Also, statistical heterogeneity was assessed with an  $I^2$  statistic. Meta-analyses were performed and forest plots were constructed using Review Manager, version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration).

#### Evaluating Quality of Bodies of Evidence

The rating of the quality of the entire body of evidence for each intervention and outcome comparison was assessed by the panel methodologist. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used for summarizing and grading the pooled evidence. Ratings of the pooled evidence started as high quality and were downgraded based on the domains of risk of bias, precision, consistency, directness, and publication bias.

A letter grade (A, B, C or Insufficient) was assigned by the panel to each pooled estimate based on the CHEST grading system (see the "Rating Scheme for the Strength of the Recommendations" field) as indicated by the evidence level of the body of literature supporting each intervention and outcome comparison. To be considered at least C-level evidence, two or more studies addressing a particular intervention and outcome were needed. However, pooled estimates were downgraded from higher evidence levels into an "Insufficient" level of evidence if indicated by domains set forth by a GRADE methodologic approach. A meta-analysis was performed only when two or more studies addressed a particular intervention and outcome. All performed meta-analyses are available in e-Figure 1, and profiled evidence is available in e-Table 2 in the Supporting Data (see the "Availability of Companion Documents" field). The study data that these pooled estimates were based upon are available in e-Table 3 in the Supporting Data (see the "Availability of Companion Documents" field).

## Methods Used to Formulate the Recommendations

#### Expert Consensus (Delphi)

## Description of Methods Used to Formulate the Recommendations

#### Composition and Selection of Topic Panel Members

For this American College of Chest Physicians (CHEST) guideline project, a nonconflicted chair was appointed by the organization's Guidelines Oversight Committee (GOC). The chair had the authority to nominate (subject to GOC review and approval) other panelists for specific roles, including participation on the project executive committee and topic editors for the various sections based on drug classes.

All panelists (consisting of the chair, executive committee members, and topic editors) were approved by the CHEST GOC after review of their qualifications and conflict of interest (COI) disclosures.

#### Drafting of Recommendations

Recommendations were drafted by the panelists assigned to each topic by the project chair, informed from the evidence gathered and aimed to be clinically relevant. Clinically relevant recommendations could not always be directly informed from the data as presented in the studies included in the evidence review. For example, the panel recognized that although changes in individual cardiopulmonary hemodynamic parameters (e.g., cardiac output [CO] or pulmonary vascular resistance [PVR]) have been reported in studies included in the evidence review, therapeutic choices would not likely be made on the basis of single hemodynamic parameters. Rather, the panel believed patterns of improvement among multiple cardiopulmonary hemodynamic variables would more likely inform sound clinical recommendations. Because the associated evidence reported outcomes only for specific variables individually (e.g., for PVR, mean pulmonary artery pressure [mPAP], CO, cardiac index, right atrial pressure) and not overall patterns of hemodynamic improvement, the panel chose not to grade recommendation statements involving cardiopulmonary hemodynamics but rather simply alert clinicians to when improvements in individual parameters have been found. Similarly, despite its limitations, assessments of a patient's World Health Organization Functional Class (WHO FC) are frequent starting points in deciding upon therapy and a basis upon which drugs are approved by the U.S. Food and Drug Administration (FDA). Accordingly, recommendations were organized according to WHO FC. Because available evidence frequently, however, did not report results specifically according to WHO FC, recommendations organized in this manner were downgraded for indirectness according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Where the evidence level was determined "A," "B," or "C," an evidence-based guideline was pursued. Where the evidence level was determined "Insufficient," a consensus statement was pursued. In these instances, "CB" (consensus-based) was considered the grade. All areas considering CCBs as a therapy were graded as CB because of insufficient evidence. Separately, a number grade (1 or 2) was assigned by the panel to each

drafted recommendation based on the CHEST grading system (see the "Rating Scheme for the Strength of the Recommendations" field). The number grade is a reflection of the topic editors' consensus on the balance of benefits and harms of treatment, based on their expert clinical knowledge, experience, and interpretation of the evidence in the gathered literature. Consensus in this instance was determined through open discussion and debate between the two authoring topic editors for each section.

Topic editors drafted initial recommendations, which were combined with the corresponding grade and presented to the entire panel via webinar. Following subsequent group discussions and wording refinements, the entire panel met in Philadelphia in May 2013 to discuss organization and consistency of the recommendations. After the recommendations were in final draft form, they were presented to the entire panel in a formal consensus development process based on the Delphi technique.

### Consensus Development

The purpose of the Delphi technique in this project was to achieve formal consensus on each recommendation while accounting for group interaction bias and maintaining anonymity among respondents. Using an online survey ([www.surveymonkey.com](http://www.surveymonkey.com)), panelists were requested to vote representing their level of agreement with each presented recommendation based on a five-point scale derived from the GRADE grid. Also, each panelist could provide open-ended feedback on each recommendation with suggested wording edits or general remarks.

Each presented recommendation or consensus-based statement was required to achieve panel consensus (80% of the votes in agreement) to be included in the final manuscript, along with a response rate of  $\geq 75\%$  of survey respondents. Otherwise, the recommendation was revised or dropped by the author, based on the anonymous and collated open-ended feedback from the respondents in the survey. If the recommendation or consensus-based statement was revised, the author had the choice to resubmit it to the next round of the survey for voting again by the entire panel. The process was continued until consensus had been reached on each of the presented statements. When the statements that achieved panel consensus had been identified through this process, the executive committee then reviewed each chapter's final recommendations and consensus based statements to resolve any areas of confusion or inconsistency before a final manuscript was submitted for the peer review process.

## Rating Scheme for the Strength of the Recommendations

### Strength of the Recommendations Grading System

Grade of Recommendation	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence, Grade 1C	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient's or societal values. Further research is very unlikely to change confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient's or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate

Weak Recommendation	Grade of Recommendation	Benefits, Risk and Burden	Evidence of Outcomes	Methodologic Quality of Supporting Evidence	Other alternatives	Implications
low- or very-low-quality evidence, Grade 2C		risks, and burden; benefits, risk, and burden may be closely balanced	case series, or RCTs, with serious flaws or indirect evidence		Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate	
Consensus-based, Grade CB		Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation		Future research may well have an important impact on confidence in the estimate of effect and may change the estimate	

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Review by American College of Chest Physicians (CHEST) and External Reviewers

When the final manuscript was completed and endorsed by the executive committee, the manuscript underwent peer review process by the organization to consider content, methods, and adherence to the organization's processes. Reviewers were self-nominated and vetted through the same conflict of interest (COI) disclosure and management process as the panelists. Reviewers were either members of the organization's Cardiovascular and Pulmonary Vascular NetWork, the CHEST Guidelines Oversight Committee (GOC), or the CHEST Board of Regents. In addition, CHEST primary reviewers from the GOC and Board of Regents and a reviewer selected by the Editor of the CHEST journal reviewed the entire article for fluency and cohesiveness.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate treatment for adult patients with pulmonary arterial hypertension (PAH)

### Potential Harms

Adverse Effects of Pharmacotherapy

- The use of calcium channel blockers (CCBs) in patients with pulmonary arterial hypertension (PAH) can cause systemic hypotension

producing reflex tachycardia, sympathetic stimulation, and right ventricular ischemia. Reports of serious adverse events when CCBs are used inappropriately underscore that CCBs need to be used with caution, and only following testing of a short-acting vasodilator to confirm the presence of vasoreactivity. Their prescription without close patient follow-up or documentation of the beneficial hemodynamic effects is not recommended. Increasing CCB doses in patients who are not vasoreactive can increase morbidity and may be fatal. CCBs at high dosages are well tolerated, with the major side effect being ankle edema, a known side effect of CCBs, which can be treated with diuretics. CCBs are not specifically approved for use in PAH by either the U.S. Food and Drug Administration (FDA) or European Medicines Agencies.

- Adverse events associated with bosentan treatment in clinical trials included abnormal liver function tests, peripheral edema, palpitations, and chest pain. Monthly monitoring of liver function tests is required for patients receiving bosentan therapy.
- Peripheral edema, headache, and nasal congestion tended to occur in certain studies more frequently in patients receiving ambrisentan than placebo, but no patients treated with ambrisentan developed serum aminotransferase concentrations more than three times the upper limit of normal.
- In a randomized, placebo-controlled phase 3 trial, the number of patients in the placebo, 3-mg macitentan, and 10-mg macitentan groups who discontinued the study drug owing to adverse events was 31 (12.4%), 34 (13.6%), and 26 (10.7%), respectively. The incidences of peripheral edema and of alanine aminotransferase or aspartate aminotransferase levels that were more than three times the upper limit of the normal range were similar across the three groups. As compared with patients who received placebo, higher percentages of patients in the two macitentan groups had nasopharyngitis, headache, and anemia. Three patients, one in each group, discontinued treatment because of anemia.
- Side effects more commonly reported with the use of intravenous (IV) epoprostenol or treprostinil than placebo include headache, jaw pain, diarrhea, abdominal pain, anorexia, vomiting, photosensitivity, cutaneous flushing, and arthralgias. Other adverse effects associated with IV prostanoid use include infection of the catheter site, catheter-related bloodstream infection and sepsis, and malfunction of the drug-delivery system. Site pain occurs frequently in those on subcutaneous treprostinil. Inhaled prostanoids result in cough, headache, flushing, nausea, and syncope more commonly than placebo with iloprost and cough, headache, and flushing more commonly than placebo with treprostinil.
- In a placebo-controlled trial, the most frequently occurring serious adverse events of riociguat were syncope (in 1% of the patients in the 2.5-mg maximum group vs. 4% in the placebo group), worsening pulmonary hypertension (in <1% of the patients in the 2.5-mg maximum group vs. 2% in the placebo group), chest pain (in 1% of the patients in both the 2.5-mg maximum group and the placebo group), and right ventricular failure (in 1% of the patients in both groups). Drug-related serious adverse events in the 2.5-mg maximum group included three cases of syncope (in 1% of the patients) and single cases of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure, and hypotension (in a total of 0.4% of the patients).

## Contraindications

### Contraindications

- Contraindications to acute vasoreactivity testing include a low systemic blood pressure (BP), low cardiac output (CO), or the presence of Functional Class (FC) IV symptoms. Acute vasoreactivity testing may be complicated by hypotension, and the misinterpretation of results may result in the inappropriate exposure of patients to the risks of a treatment trial with calcium channel blockers (CCBs) without the possibility of clinical benefit.
- Estrogen-containing contraceptives may increase the risk of venous thromboembolism (VTE) and are not recommended for women with childbearing potential who have pulmonary arterial hypertension (PAH). Additionally, bosentan may decrease the efficacy of hormonal contraception. Bosentan, ambrisentan, macitentan and riociguat are contraindicated in pregnancy (category X; evidence of serious fetal abnormalities) and dual mechanical barrier contraceptive techniques are recommended in female patients of childbearing age taking these medications.

## Qualifying Statements

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- CHEST guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at

the [CHEST Web site](#) .

- This document aims to provide practical guidance to clinicians faced with common questions regarding the use of available pharmacotherapies for the treatment of patients with pulmonary arterial hypertension (PAH). The panel sought to apply a rigorous process to the collection and assessment of evidence and to make guideline recommendations informed and supported by that evidence. Unfortunately, rigorous data needed to address important questions faced by clinicians when treating patients with PAH are often absent or insufficient. They therefore present a hybrid document. When sufficiently strong evidence from randomized clinical trials addressing a clinically important question is available, the panel has based its guideline recommendation statements upon them. When evidence is absent or insufficient to provide evidence-based guideline recommendation statements, they provide their best expert advice as consensus statements with the goal of helping clinicians navigate important therapeutic questions.
- Standards for the development of clinical guidelines have evolved, and the approach to the grading of evidence has become more rigorous since the last CHEST guideline on PAH. As a result, readers may note lower grades assigned to recommendations in this guideline update as compared with the grading of statements recommending similar actions in prior CHEST guidelines on PAH or related recommendations of other organizations. This may seem paradoxical at first, as the evidence upon which the recommendations are based remains, in many cases, largely the same. The change in grading reflects the more rigorous standard now being applied by CHEST to the evaluation of evidence. Further, some equivalent and parallel trials of individual drugs have been conducted and reported independently, whereas others were reported as single larger investigations. We recognize that this may influence assessments of the overall strengths of evidence available, but we judged it best to adhere to a consistent approach based upon how studies were accepted by the U.S. Food and Drug Administration (FDA) and reported.
- This guideline addresses only drugs that were approved by the FDA for the management of PAH symptoms at the time that the guideline was developed (with the exception of calcium channel blockers [CCBs], which were included because of their continued importance as PAH-specific therapy for a small but important subgroup of patients with PAH). Further, as the FDA has approved drugs for PAH therapy in part according to a patient's World Health Organization (WHO) functional classification, and because the panel believes it will best assist clinicians to use this guideline, the panel has organized recommendations around such a classification. The panel recognizes the limitations of the WHO functional classification and that other variables must be considered simultaneously (such as exercise capacity, right ventricular function, hemodynamics, economic and other social factors, quality of life, and, most importantly, patient preferences). The panel recognizes also the limitations of the hemodynamic, exercise capacity (6-min walk distance [6MWD]), and clinical worsening end points that are presented in this guideline for clinicians to consider when choosing pharmacologic therapy. Knowledge of the relative importance of these end points and how changes in each or groups of end points impact patients' lives is limited.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

## Identifying Information and Availability

### Bibliographic Source(s)

Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, Palevsky HI, Rich S, Sood N, Rosenzweig EB, Trow TK, Yung R, Elliott CG, Badesch DB. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest*. 2014 Aug;146(2):449-75. [90 references] [PubMed](#)

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2014 Aug

### Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

### Source(s) of Funding

The guideline was funded in total by internal funds from the American College of Chest Physicians.

### Guideline Committee

Expert Panel

### Composition of Group That Authored the Guideline

*Expert Panel:* Darren B. Taichman, MD, PhD, FCCP; Joe Ornelas, MS; Lorinda Chung, MD; James R. Klinger, MD, FCCP; Sandra Lewis, PhD; Jess Mandel, MD; Harold I. Palevsky, MD, FCCP; Stuart Rich, MD, FCCP; Namita Sood, MD, FCCP; Erika B. Rosenzweig, MD; Terence K. Trow, MD, FCCP; Rex Yung, MD, FCCP; C. Gregory Elliott, MD, FCCP; David B. Badesch, MD, FCCP

### Financial Disclosures/Conflicts of Interest

For one of the 12 approved panelists (who had relevant conflicts), a conflicts of interest (COI) management program was followed according to the procedures of the Guidelines Oversight Committee (GOC), including abstention from voting on areas related to conflicts (see e-Table 1 in the Supporting Data [see the "Availability of Companion Documents" field]). Throughout the guideline development process all panelists were required to report any new activities that might involve potential COIs for review and approval by the GOC.

#### Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following conflicts of interest: Until 2009, Dr Taichman was an employee of the University of Pennsylvania, which received research grant support from Actelion Pharmaceuticals Ltd for participation in the Registry to Evaluate Early and



Long-term Pulmonary Arterial Hypertension (PAH) Disease Management (REVEAL Registry). He received honoraria for continuing medical education (CME) talks sponsored by the Pulmonary Hypertension Association. Since 2009, he has been an employee of the American College of Physicians. Dr Chung receives grant funding from the Scleroderma Research Foundation. She has received compensation for clinical trial patient enrollment from Gilead; Actelion Pharmaceuticals Ltd; United Therapeutics Corp; Pfizer Inc; MedImmune LLC; Genentech, Inc; and InterMune. She has participated in speaking activities for Actelion Pharmaceuticals Ltd and Gilead and has served on the Advisory Board for Gilead. Dr Lewis is an officer in an institution that probably has a financial relationship with a commercial entity having an interest in the subject of this manuscript. However, the time of working on this manuscript did not overlap with the time she has been employed by this company. She also makes public statements on guideline methodology. Dr Klinger has served as a site investigator for numerous clinical studies in pulmonary hypertension and in numerous pharmacologic, industry-sponsored studies in pulmonary hypertension. Dr Klinger has served as a consultant for Bayer and United Therapeutics Corp. He has served on the steering committee and adjudication committee for industry-sponsored clinical trials. He has received grant support from the National Institutes of Health (NIH) for enrollment of patients in clinical registries. Dr Mandel receives royalties as an author and editor from Elsevier BV and Wolters-Kluwer. Dr Palevsky has within the past 3 years served as a consultant for Actelion Pharmaceuticals Ltd, Bayer AG, Gilead, and United Therapeutics Corp, and has served on data and safety monitoring boards for Aires Therapeutics and Pfizer Inc. He has also served as a grant reviewer for the Entelligence PAH Young Investigators Award Program and has given continuing medical education and other PAH lectures. Dr Rich has received money for speaker's fees from GlaxoSmithKline. Dr Rich has no other intellectual or financial conflicts to disclose. While he had worked in industry in the past, this ended in 2006. Dr Sood has received pharmaceutical grant money for research products and serves as a consultant for advisory board meetings for Actelion Pharmaceuticals Ltd, Bayer AG, Gilead, and United Therapeutics Corp. Dr Rosenzweig has received honoraria from Actelion, Gilead Science, and United Therapeutics as an advisor on Scientific Advisory Board Panels and Ikaria for a study oversight committee in the past three years. Dr Trow has in the distant past served as a consultant for Bayer AG, Actelion Pharmaceuticals Ltd, Gilead, and United Therapeutics Corp. He also used to serve on Speaker's Bureaus for Actelion Pharmaceuticals Ltd, Gilead, and United Therapeutics Corp. No such talks have been given in the 2.5 years prior to this publication. In addition, Dr Trow has served as the primary investigator on the COMPASS (Effects of Combination of Bosentan and Sildenafil vs Sildenafil Monotherapy on Morbidity and Mortality in Symptomatic Patients with PAH) 2 trial and Registry to Prospectively Evaluate Use of Ventavis in Patients With PAH (RESPIRE Registry), which have now finished. Dr Elliott is employed by Intermountain Healthcare (IHC Health Service, Inc) and IHC Health Services, Inc has received compensation trials (on which he is the principal investigator) from Actelion Pharmaceuticals Ltd, Bayer AG, Genentech, Gilead, and United Therapeutics Corp. Dr Elliott serves on the End-Point Adjudication Committee for a study sponsored by Lung LLC. Both he and IHC Health Services received compensation for his service on the End-Point Adjudication Committee. He has received travel and reimbursement for meetings he attended sponsored by Bayer AG, Lung LLC, and Ikaria. He serves as a consultant to Bayer Pharmaceuticals. He received honoraria for serving on the REVEAL Steering Committee, which was supported by CoTherix/Actelion. He serves on the board of directors for the Pulmonary Hypertension Association, served on the American College of Chest Physicians Consensus Guidelines Committee for Pulmonary Arterial Hypertension, and is an advisor for the Scientific Leadership Council of the Pulmonary Hypertension Associations. Dr Badesch has received honoraria for service on steering committees or advisory boards (or as a consultant) to the following companies working in the area of pulmonary hypertension: Actelion Pharmaceuticals Ltd/CoTherix; Gilead; Pfizer Inc; United Therapeutics Corp/Lung Rx; Bayer AG; Ikaria, Inc; and Arena Pharmaceuticals, Inc. He has received grant support for clinical studies from Actelion Pharmaceuticals Ltd/CoTherix; Gilead; Pfizer Inc; United Therapeutics Corp/Lung Rx; Bayer AG; Novartis AG; Ikaria, Inc; and Reata Pharmaceuticals Inc. He provided information pertinent to a legal matter for Actelion Pharmaceuticals, Inc. Mr Ornelas and Dr Yung have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

## Guideline Endorser(s)

Pulmonary Hypertension Association - Disease Specific Society

## Guideline Status

This is the current release on the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: Available to subscribers of [Chest - The Cardiopulmonary and Critical Care Journal](#) .

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL

## Availability of Companion Documents

The following are available:

- Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Supporting data. 2014 Aug. 25 p. Electronic copies: Available from [Chest - The Cardiopulmonary and Critical Care Journal Web site](#) .
- McCrory DC, Coeytaux RR, Schmit KM, Kraft B, Kosinski AS, Mingo AM, Vann LM, Gilstrap DL, Hargett CW, Lugogo NL, Heidenfelder BL, Posey R, Irvine RJ, Wing L, Pendergast K, Dolor RJ. Pulmonary arterial hypertension: screening, management, and treatment. Comparative effectiveness review no. 117. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC087-EF. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Apr. 391 p. Electronic copies: Available from the [AHRQ Web site](#) .
- Pulmonary arterial hypertension: new CHEST guidelines and new CDC report. Podcast. 2014 Aug. Available from [Chest - The Cardiopulmonary and Critical Care Journal Web site](#) .

## Patient Resources

None available

## NGC Status

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